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10/766,011	01/29/2004	Masataka Andoh	Q79665	2008

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EXAMINER	
SKOWRONEK, KARLHEINZ R	
ART UNIT	PAPER NUMBER
1631	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/766,011	ANDOH ET AL.	
	Examiner	Art Unit	
	Karlheinz R. Skowronek	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12-26-2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,17 and 18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8, 17 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

Claims 1-18 are pending.

Claims 9-16 stand withdrawn as being directed to a non-elected invention.

Claims 1-8, 17 and 18 are being examined.

Response to Arguments

Applicants' arguments to the objections/rejections stated in the previous office action have been fully considered and are persuasive in part. Rejections not reiterated hereby withdrawn. The following rejections constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear what the variables in claim 4 are intended to represent. For example, the variable μ, in statistics, is commonly representative of a mean. However, in claim 4 μ appears to not to be a mean. The other variables recited in claim 4 are similarly vague. The variables of claim 4 are also used in dependent claim 5-7 and thus claims 5-7 are also vague.

Claim 5-8 also rejected because they depend from claim 4, and thus contain the above issues due to said dependence.

Claim 5 is unclear regarding the variable "nu" (ν). What does "Nu" represent in equation 30? Is the variable a Nu or a "v"? How is "Nu" different from "v"?

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 17, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over McLachlan et al. (The EMMIX software for the fitting of mixtures of normal and t-Components and the user's guide to EMMIX-version 1.3 1999, Journal of Statistical Software. Vol. 4(2), p. 1-14, 12 July 1999, [www.jstatsoft.org]){McLachlan 1999} or McLachlan et al (Bioinformatics Vol. 18, No. 3, p. 413-422, 2002){McLachlan 2002}, in view of Peel et al (Statistics and Computing, Vol. 10, p. 339-348, 2000) {Peel 2000} and further in view of Lee et al (PNAS, Vol. 97, No. 18, p. 9834-9839, 2000) {Lee 2000}.

The claims are drawn to a system, computer program and a computer readable medium for estimating gene expression probabilities in which distributed parameters of a mixed normal distribution are determined from gene expression data are determined

by the equation: $(1-\xi)\varphi(u-\mu_0|\sigma_0^2)+\xi\varphi(u-\mu_1|\sigma_1^2)$ (25) where $\varphi(u-\mu|\sigma^2)$ represents the density function of a one-dimensional normal distribution with average μ_1 and variance σ_0^2, $(\mu_0|\sigma_0^2)$ and $(\mu_1|\sigma_1^2)$ are average and variance parameters of first and second components, respectively, and ξ is the mixing ratio, with the assumption that $\mu_0 < \mu_1$, $\sigma_0^2 > 0$, $\sigma_1^2 > 0$, $0< \xi <1$ is satisfied, mixing ratio parameter estimating means for estimating a mixing ratio parameter of the mixed normal distribution using the gene expression level data sent from said input device and the distributed parameters sent from said distributed parameter estimating means, and sending the estimated mixing ratio parameter, and posterior probability calculating means for calculating the posterior probability of the expression state of each gene in each channel using the gene expression level data, the estimated distributed parameters and mixing ratio parameter, and sending the calculated posterior probability to said output device.

McLachlan 1999 teach a gene expression state estimating system (The system is describe in the User's Guide to EMMIX on p. 4, paragraph 1, "systems") for estimating the probability of gene expression in each channel, the system including an input device for sending gene expression level data, a program-controlled data analyzer, and an output device, wherein said data analyzer comprises distributed parameter estimating means for estimating distributed parameters of a mixed normal distribution shown in the following equation (25) (in general form as equation 1, p. 2) using the gene expression level data from said input device, and sending the estimated distributed parameters: $(1-\xi)\varphi(u-\mu_0|\sigma_0^2)+\xi\varphi(u-\mu_1|\sigma_1^2)$ (25) where $\varphi(u-\mu|\sigma^2)$ represents the density function of a one-dimensional normal distribution with average μ_0 and

variance σ^2, $(\mu_0|\sigma_0^2)$ and $(\mu_0|\sigma_1^2)$ are average and variance parameters of first and second components, respectively, and ξ is the mixing ratio, with the assumption that $0< \xi <1$ is satisfied (Examples, p. 10, paragraph 1), mixing ratio parameter estimating means for estimating a mixing ratio parameter of the mixed normal distribution using the gene expression level data sent from said input device and the distributed parameters sent from said distributed parameter estimating means ("mixing proportions", p. 6, paragraph 2), and sending the estimated mixing ratio parameter, and posterior probability calculating means for calculating the posterior probability of the expression state of each gene in each channel using the gene expression level data, the estimated distributed parameters and mixing ratio parameter, and sending the calculated posterior probability to said output device ("current estimate of posterior probability, p. 6, top of page; and p. 33 of the User's guide to EMMIX, first line of text).

The equation taught by McLachlan 1999 and Mclachlan 2000, $f(\boldsymbol{y};\Psi)=\sum_{i=1}^{g}\pi_i c_i(\boldsymbol{y};\theta_i)$ for estimating the distributed parameters can be expressed as equation 25 of the instant application in the case of 2 conditions. McLachlan 1999 define the variable π as the mixing ratio parameter that, in the instant case, is represented by the variable ξ. McLachlan 1999 teach the mixing ratio parameters sum to 1, thus when considering 2 conditions, the mixing ratio for each condition can be represented by π and $(1-\pi)$. McLachlan 1999 teach that in the case of normal mixture model, $c_1(\mathbf{y};\theta_1)$ can be expressed as the probability density function $\phi(\mathbf{y};\mu_i, \Sigma_i)$ where μ and Σ represent the mean and covariance matrix reading on the variables average μ_0 and variance σ^2, thus

the general equation can be rewritten as $(1-\pi)\phi(\mathbf{y};\mu_0, \Sigma_0) +\pi\phi(\mathbf{y};\mu_1, \Sigma_1)$ for 2 component mixture model and is the equation 25 of the instant application, $(1-\xi)\varphi(u-\mu_0|\sigma_0^2)+ \xi\varphi(u-\mu_1|\sigma_1^2)$.

McLachlan 1999 teach the gene expression program of claim 17 (FORTRAN, p. 3, paragraph 3) and is further described by McLachlan et al. in the User's guide to EMMIX.

McLachlan 1999 teach the computer readable medium of claim 18 which was provided by McLachlan 1999 along with the description of the system and is freely available through the publisher internet address above.

Mclachlan 1999 and Mclachlan 2000 do not explicitly teach the derivation of the equation 25.

Both Peel 2000 and Lee 2000 explicitly teach equation 25.

Peel teaches how it is derived from the multivariate form and describes the claimed equation as equation 3 (p. 340, col 2).

Lee 2000 teaches the same equation as equation 2. In Lee 2000, the two component mixed normal equation has different variables, but is the same equation. Lee 2000 describes the variable p as a probability. This is read and interpreted as a mixing ratio because in the case of two outcomes (as is the case in Lee 2000). The probability of one outcome occurring is p and the probability of the one outcome not-occuring is 1-p. Since any outcome may or may not occur, the probabilities of both possibilities (occurring v. not-occuring) must equal 1, ie. the outcome is expressed as a mixture of occurring and not-occuring. The functions $f_u(y)$ and $f_e(y)$ are probability

density functions (pdf) as similarly describe in Peel 2000 and McLachlan 2002/1999 (p. 9835, para 1, col. 2). Lee 2000 teaches the function $f_u(y)$ can be expressed as Y_g and is distributed as $N(\mu_u, \sigma_u^2)$ representing the unexpressed outcome and $f_e(y)$ can be expressed as Y_g and is distributed as $N(\mu_e, \sigma_e^2)$ representing the expressed outcome (p. 9835, para 1, col. 2). Together the terms $f_u(y)$ and $f_e(y)$ can be expressed $f_u(y) = \varphi(Y_g-\mu_u|\sigma_u^2)$ and $f_e(y) = \varphi(Y_g-\mu_e|\sigma_e^2)$ reading on the pdf $\varphi(u-\mu_0|\sigma_0^2)$ and $\varphi(u-\mu_1|\sigma_1^2)$ of the instant application because Lee 2000 teaches the events of expression and not expressing are complementary (p. 9835, para 2, col. 2, line 1-3). Lee 2000 requires that $\mu_u<\mu_e$ (9835, para 1, col. 2).

It would have been obvious to one of skill in the art to combine the methods for estimating the probability of gene expression of McLachlan 1999, McLachlan 2000, Peel 2000, and Lee 2000 because the methods all use the same equation for the same purpose, namely to estimate gene expression using statistical means.

One would have had a reasonable expectation of success because Lee 2000 demonstrate the successful use of the method and McLachlan 2000 demonstrate the success of the system and software to analyze gene expression data.

Claim 2, 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over McLachlan et al. (The EMMIX software for the fitting of mixtures of normal and t-Components and the user's guide to EMMIX-version 1.3 1999, Journal of Statistical Software. Vol. 4(2), p. 1-14, 12 July 1999, [www.jstatsoft.org]){McLachlan 1999} or McLachlan et al (Bioinformatics Vol. 18, No. 3, p. 413-422, 2002){McLachlan 2002}, in

view of Peel et al (Statistics and Computing, Vol. 10, p. 339-348, 2000) {Peel 2000} and further in view of Lee et al (PNAS, Vol. 97, No. 18, p. 9834-9839, 2000) {Lee 2000} as applied to claim 1 above, and further in view of Pan et al (Genome Biology, vol. 3, no2, p. research0009.1–0009.8, 29 Jan 2002).

Claim 2 is directed to estimating mixing ratio, average, and variance by applying the mixed normal distribution of two component data from two channel data in a region where the difference between channels is near zero.

McLachlan 1999, McLachlan 2000, Peel 2000, and Lee 2000 do not explicitly teach the limitations of claim 2.

Pan teaches estimating mixing ratio, average, and variance by applying the mixed normal distribution of two component data (p. 3, col 2, lines 6-11) for data from a region where the difference is near zero. Figure 2 from Pan shows a comparison in which the data is near zero which is seen to fairly read on the limitations of claim 2. Pan teaches the gene expression levels under two conditions(channels) (p. 3, col. 1)

It would have been obvious for one of skill in the art to combine the estimates of Pan with the mixed normal distribution models of McLachlan 1999, McLachlan 2000, Peel 2000, and Lee 2000 because Pan teaches that model based clustering is a powerful method that is useful in analyzing gene expression data.

One would have had a reasonable expectation of success because Pan successfully demonstrate the use of mixed normal distribution models.

Claim 3 is drawn to a median of the difference between channels 1 and 2 for each measurement.

Lee 2000 teaches the median which reads on claim 3 (p. 9835, col. 1, sect 2).

It would have been obvious to use the median of Lee 2000 with the mixed normal distribution calculations of McLachlan 1999, McLachlan 2000, Peel 2000, and Pan because each of McLachlan 1999, McLachlan 2000, Peel 2000, Pan and Lee 2000 calculated mixed normal distributions of micro array data and lee teaches that statistical analysis have demonstrated important insights into the nature of inherent variability (p9834, col 1, para 1,last sentence).

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karlheinz R. Skowronek whose telephone number is (571) 272-9047. The examiner can normally be reached on Mon-Fri 8:00am-5:00pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karlheinz R. Skowronek/

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PRIMARY EXAMINER